

Preoperative REM Sleep Behavior Disorder and Subthalamic Nucleus Deep Brain Stimulation Outcome in Parkinson Disease 1 Year After Surgery

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Abstract

Background and Objectives

To determine whether patients with Parkinson disease (PD) eligible for subthalamic nucleus deep brain stimulation (STN-DBS) with probable REM sleep behavior disorder (RBD) preoperatively could be more at risk of poorer motor, nonmotor, and quality of life outcomes 12 months after surgery compared to those without RBD.

Methods

We analyzed the preoperative clinical profile of 448 patients with PD from a French multicentric prospective study (PREDISTIM) according to the presence or absence of probable RBD based on the RBD Single Question and RBD Screening Questionnaire. Among the 215 patients with PD with 12 months of follow-up after STN-DBS, we compared motor, cognitive, psycho-behavioral profile, and quality of life outcomes in patients with (pre-opRBD+) or without (pre-opRBD-) probable RBD preoperatively.

Results

At preoperative evaluation, pre-opRBD+ patients were older (61 ± 7.2 vs 59.5 ± 7.7 years; $p = 0.02$), had less motor impairment (Movement Disorder Society–sponsored version of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS] III "off": 38.7 ± 16.2 vs 43.4 ± 7.1 ; $p = 0.03$) but more nonmotor symptoms on daily living activities (MDS-UPDRS I: 12.6 ± 5.5 vs 10.7 ± 5.3 ; $p < 0.001$), had more psychobehavioral manifestations (Ardouin Scale of Behavior in Parkinson's Disease total: 7.7 ± 5.1 vs 5.1 ± 0.4 ; $p = 0.003$), and had worse quality of life

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Predistim Study Group coinvestigators are listed at links.lww.com/WNL/B590

Glossary

ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; **ICD**; **impulse control disorder**; **LEDD** = levodopa equivalent daily dose; **MDS-UPDRS**; **Movement Disorder Society Unified Parkinson's Disease Rating Scale**; **MoCA** = Montreal Cognitive Assessment; **PD**; **Parkinson disease**; **PDQ-39** = Parkinson's Disease Questionnaire-39; **PDQ-39-SI**; **Parkinson's Disease Questionnaire-39 Summary Index**; **pre-opRBD+** = with probable REM sleep behavior disorder preoperatively; **pre-opRBD-**; **without probable REM sleep behavior disorder preoperatively**; **RBD** = REM sleep behavior disorder; **RBD-1Q**; **RBD Single Question**; **RBD-SQ** = RBD Screening Questionnaire; **SDMT**; **Symbol Digit Modalities Test**; **STN-DBS** = subthalamic nucleus deep brain stimulation.

(Parkinson's Disease Questionnaire-39: 33 ± 12 vs 29 ± 12 ; $p = 0.03$), as compared to pre-opRBD- patients. Both pre-opRBD+ and pre-opRBD- patients had significant MDS-UPDRS IV score decrease (-37% and -33% , respectively), MDS-UPDRS III "med 'off/stim 'on" score decrease (-52% and -54%), and dopaminergic treatment decrease (-52% and -49%) after surgery, with no between-group difference. There was no between-group difference for cognitive and global quality of life outcomes.

Conclusions

In patients with PD eligible for STN-DBS, the presence of probable RBD preoperatively is not associated with a different clinical outcome 1 year after neurosurgery.

Trial Registration Information

NCT02360683.

Classification of Evidence

This study provides Class II evidence that in patients with PD eligible for STN-DBS, the presence of probable RBD preoperatively is not associated with poorer outcomes 1 year post surgery.

Recent evidence suggests that patients with Parkinson disease (PD) who have REM sleep behavior disorder (RBD) might exhibit a more severe phenotype,¹ including greater motor disabilities and axial symptoms,^{1,2} dysautonomia,³ cognitive impairment,^{4,5} visual hallucinations,⁶ and impulse control disorders.^{7,8} Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-documented treatment for severe PD with motor fluctuations and dyskinesias.⁹⁻¹¹ However, some patients may demonstrate worsening of other symptoms following STN-DBS, such as apathy,¹⁰ emergence of impulsive behaviors,¹⁰ and axial symptoms including freezing of gait, postural instability, and dysarthria.¹²⁻¹⁴ Neuroimaging indicators have been proposed for guiding surgical decisions for DBS, such as connectivity profile,¹⁵ lower boundaries of T2 relaxometry in the STN reported to predict motor outcome,¹⁶ or accumbens nucleus volume reported as a marker of risk of cognitive decline after STN-DBS.¹⁷ Those tools are difficult to use in daily practice and identifying patients at risk of negative outcomes after STN-DBS remains a challenge because there are few clinical indicators to determine patients most likely to benefit from this treatment.^{18,19} Until recently, only 2 monocentric studies (conducted in 41 and 50 patients, respectively) have assessed outcomes of patients with PD with RBD undergoing STN-DBS, and reported conflicting results.^{20,21}

The aim of this study was to investigate whether the presence of RBD before STN-DBS could affect motor, cognitive,

psycho-behavioral, and quality of life outcomes 12 months after STN-DBS, using a large French prospective cohort of patients with PD, and to characterize the preoperative profile of patients with PD with and without probable RBD.

Methods

Patients

This study was an ancillary analysis using data collected from the PREDISTIM cohort. PREDISTIM is an ongoing prospective multicentric cohort (Protocol 2013-A00193-42) sponsored by the University Hospital of Lille, conducted in 17 PD expert centers from the French clinical research network (NS-Park/F-CRIN). The primary objective was to study predictive factors of the therapeutic response to STN-DBS on long-term quality of life. Briefly, patients undergoing STN-DBS in each of the participating centers were consecutively included into the study between November 2013 and September 2019. The inclusion criteria were a diagnosis of PD according to the UK Parkinson's Disease Brain Bank, disease duration ≥ 5 years, age between 18 and 75 years, and indication for STN-DBS. Exclusion criteria included atypical parkinsonism, severe cognitive impairment, severe psychiatric disorders, acute levodopa motor response $< 30\%$, and contraindications to surgery. Clinical data were collected at baseline and then at 1 year postsurgery.

Among 795 patients enrolled in the PREDISTIM cohort and awaiting STN-DBS at the time of the analysis (February 2019), 56% (n = 448) completed RBD Screening Questionnaire (RBD-SQ) or RBD Single Question (RBD-1Q) preoperatively and were included in our ancillary study. RBD questionnaires were not initially part of the PREDISTIM study and this ancillary study began in April 2015. The clinical and demographic characteristics of patients with PD with probable RBD preoperatively (pre-opRBD+) and without probable RBD preoperatively (pre-opRBD-) were described in the whole population (n = 448). Then we investigated the outcomes 12 months after STN-DBS, in terms of variations of motor, nonmotor, and quality of life scores compared to baseline, in a subset of patients (n = 215) who had both pre- and postoperative evaluations (eFigure 1, links.lww.com/WNL/B589). Data from patients with preoperative screening of probable RBD were included into the analysis.

The primary research question of this ancillary study was whether patients with PD with probable RBD preoperatively could be more at risk of poorer motor, nonmotor, and quality of life outcomes 12 months after STN-DBS (Level of evidence: Class II).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by CPP (Comité de Protection des Personnes) Nord Ouest-IV Ethical Committee and registered in the ClinicalTrials.gov website (NCT02360683). Patients gave written informed consent, the study was conducted according to good clinical practice and local regulations, and data collection was compliant with General Data Protection Regulation (GDPR) rules.

Study Design and Clinical Scores

The diagnosis of probable RBD was assessed preoperatively using both RBD-1Q and RBD-SQ scores, which are validated as sensitive and specific tools for detecting RBD in the general population^{22,23} and in PD.^{24,25} Probable preoperative RBD (pre-opRBD+) was defined by a positive response on RBD-1Q or a score ≥ 6 on RBD-SQ at preoperative evaluation.^{22,25} Clinical assessments at each visit included collection of demographic data, parkinsonism, neuropsychological testing, quality of life questionnaires, and medical and treatment history. Parkinsonism evaluation was performed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS),²⁶ which assesses nonmotor and motor experiences of daily living (MDS-UPDRS I, II), motor examination (MDS-UPDRS III), and motor complications (MDS-UPDRS IV). MDS-UPDRS parts I-IV were performed in "off" and "on" state during a standardized acute levodopa challenge.

At baseline, motor assessment was performed using MDS-UPDRS Part III in the "off" state after 12-hour withdrawal of antiparkinsonian medication (med "off") and in the "on" state after taking 1.5 times the usual morning levodopa dose using

dispersible levodopa (med "on"). Twelve months after surgery, the efficacy of STN-DBS and of levodopa was assessed in the morning after at least 12 hours of withdrawal of antiparkinsonian medication using MDS-UPDRS Part III in 3 conditions: medication off-stimulation off (med-off/stim-off), medication off-stimulation on (med-off/stim-on), and medication on-stimulation on (med-on/stim-on). Comparison between baseline and 12 months after surgery was performed for MDS-UPDRS III "off," defined by the conditions med-off preoperatively vs med-off/stim-off postoperatively, and for MDS-UPDRS III "on," defined by the conditions med-on preoperatively vs med-on/stim-on postoperatively. The effect of chronic STN-DBS was also evaluated comparing MDS-UPDRS III in med-off condition preoperatively vs med-off/stim-on postoperatively. The axial score was defined as the sum of the following motor subscores: speech, gait, posture, and postural stability (items 18, 28, 29, and 30 on the MDS-UPDRS Part III).²⁷

Cognitive functions were assessed using 11 validated tests in PD, according to the French consensus for the evaluation of cognitive functions in PD,²⁸ which included the following: Montreal Cognitive Assessment (MoCA) for global efficiency²⁹; Symbol Digit Modalities Test (SDMT) for attention and working memory; Digit Span Forward and Backward, subtests 16-item Free/Cued Recall Test and 10/36 Spatial Recall Test for episodic memory; Oral Letter-Number Sequencing task and D-KEFS Color-Word Interference Test for executive function; Benton Judgement of Line Orientation and CLOX clock-drawing test for visuospatial function; and Boston Naming Test and Animal fluency test for language. Regarding psycho-behavioral symptoms, we used the French version of the Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) to assess hypo- and hyperdopaminergic disorders, nonmotor fluctuations, and impulse control disorder (ICD) (compulsive eating, hobbyism, punting, compulsive shopping, pathologic gambling, hypersexuality, and dopaminergic addiction).³⁰ For this scale, higher scores indicate worse mood and behavioral disturbances. The Parkinson's Disease Questionnaire-39 (PDQ-39) scale was used to assess quality of life. The PDQ-39 summary index (PDQ-39-SI) ranges from 0 to 100; higher score indicates worse quality of life.³¹

The levodopa equivalent daily dose (LEDD) was provided for each patient taking account of levodopa treatments, dopamine agonists, and other antiparkinsonian drugs such as MAO-B inhibitors, COMT inhibitors, and amantadine.³²

Statistical Analysis

Continuous data were expressed as mean and SD or median and interquartile range according to statistical distribution. The assumption of normality was assessed by the Shapiro-Wilk test. Regarding nonrepeated measures (such as comparison of baseline features between pre-opRBD+ and pre-opRBD-), continuous variables were compared between groups by Student *t* test or Mann-Whitney test when

the assumptions of *t* test were not met. Homoscedasticity was analyzed using the Fisher-Snedecor test. Categorical measures were compared between groups using χ^2 or Fisher exact tests. To compare baseline and 1 year after STN-DBS variations between pre-opRBD+ and pre-opRBD-, random-effects models were performed to measure time and group (pre-opRBD+ and pre-opRBD-) effects and their interaction time \times group, taking into account between- and within-patient variability (subject as random effect). This interaction corresponds to the difference of variation (absolute change between baseline and evaluation at M12) between pre-opRBD+ and pre-opRBD-. The normality of residuals from these models was studied using the Shapiro-Wilk test. When appropriate, a logarithmic transformation has been proposed to achieve the normality of dependent outcomes. Then, multivariate analyses were performed using adjustment on covariates fixed according to the univariate results and to the clinical relevance: age, sex, preoperative LEDD, preoperative MDS-UPDRS III "off" scores, and baseline values of studied dependent outcomes. Random-effects models were also carried out to analyze intragroup variation for pre-opRBD+ and pre-opRBD- patients. A sensitivity analysis was conducted to evaluate the statistical nature of missing data and their potential effect on results. More precisely, patients with and without follow-up at 1 year were compared for their baseline characteristics. As data were missing completely at random regarding each clinical variable, no imputation of data was applied.

Statistical analyses were performed using Stata software, version 15 (StataCorp). The tests were 2-sided, with a type I error set at 5%. As analyses were exploratory, the individual *p* values have been reported without applying systematically mathematical correction according to several works reported in the literature, but specific attention was given to the magnitude of differences and to clinical relevance.^{33,34} Indeed, it has been previously suggested that the choice and the number of tested hypotheses may be data dependent, which means that multiple significance tests can be used for descriptive purposes but not for decision making, regardless of whether multiplicity corrections are performed or not. Significant results based upon exploratory analyses should be clearly labeled as exploratory results. Conversely, the lack of multiple correction of the type I error cannot affect nonsignificant results.³⁵

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Patient Characteristics

Among 795 patients with PD enrolled in the PREDISTIM cohort and awaiting STN-DBS, 448 completed RBD-SQ or

RBD-1Q preoperatively. Out of them, 330 patients underwent surgery at the time of our study, and 215 had a postoperative evaluation 12 months after STN-DBS (eFigure 1, links.lww.com/WNL/B589).

Demographic and Clinical Profile of PD Candidates for STN-DBS at Preoperative Evaluation According to the Presence of Probable RBD Preoperatively

We characterized the demographic and clinical profile of RBD+ and RBD- preoperatively in the whole group (*n* = 448) (300 male; mean age 63.3 ± 7.4 years; mean disease duration 11.0 ± 4.3 years). Among 448 patients with PD at baseline, 242 (54%) were pre-opRBD+, while 206 were pre-opRBD-. Motor symptoms, nonmotor symptoms, and quality of life of pre-opRBD+ and pre-opRBD- patients before STN-DBS are presented in Table 1.

Pre-opRBD+ patients were older (*p* = 0.02), with a higher MDS-UPDRS I score (*p* < 0.001) and lower MDS-UPDRS III score assessed in "med-off" condition (*p* = 0.003) compared to pre-opRBD- patients.

Regarding psycho-behavioral characteristics, ASBPD total score was significantly higher in pre-opRBD+ compared to pre-opRBD- (*p* = 0.03). When considering each dimension of the scale, we observed higher scores in pre-opRBD+ for hypodopaminergic symptoms (*p* < 0.001). In contrast, non-motor fluctuations and hyperdopaminergic behaviors (including ICD subscores) did not differ between groups.

PDQ-39-SI score was significantly higher in pre-opRBD+ compared to pre-opRBD- (*p* = 0.03), specifically for emotional well-being (*p* < 0.01), communication (*p* = 0.02), social support (*p* < 0.01), cognition (*p* < 0.01), and bodily discomfort (*p* < 0.01) subscores.

Clinical Outcomes of Patients With PD After STN-DBS According to the Presence of Probable RBD Preoperatively

Analyses of clinical scores at 12 months and variation of scores between baseline and 12 months were performed on 215 patients (142 male; mean age: 60.3 ± 7.1 years; mean disease duration: 11.4 ± 4.4 years). To rule out different profile of this sample compared to the whole group, we compared demographic and clinical characteristics of both groups (Table 2). The groups with and without follow-up at 12 months were comparable for all clinical data except for MDS-UPDRS I, which was lower, and MoCA, which was greater, in the group with a postoperative assessment (respectively 11.1 ± 5.1 vs 12.2 ± 5.7 ; *p* = 0.003 for MDS-UPDRS I and 26.8 ± 2.3 vs 25.8 ± 3.2 ; *p* < 0.001 for MoCA), although nonsignificant clinical size effect.

Among 215 patients with PD who were assessed both preoperatively and 12 months after STN-DBS, 122 (57%) were pre-opRBD+, while 93 (43%) were pre-opRBD-. Parkinsonian,

Table 1 Clinical and Demographic Features of Patients With Parkinson Disease Who Are Candidates for Subthalamic Nucleus Deep Brain Stimulation at Preoperative Assessment, According to the Presence or Absence of Probable REM Sleep Behavior Disorder Preoperatively (pre-opRBD)

Characteristics	pre-opRBD+ (n = 242)	pre-opRBD- (n = 206)	p Value
Sex, male: female	169:73	131:75	0
Age, y	61.0 ± 7.2	59.5 ± 7.7	0.02
Total LEDD, mg/d	1,330 (1,074–2,252)	1,324 (963–1,696)	0.58
Dopamine-agonist LEDD, mg/d	240 (150–356)	300 (160–460)	0.06
Duration of disease, y	11.3 ± 4.5	10.8 ± 4.1	0.32
Duration since onset motor complications, y	6.0 ± 3.6	5.9 ± 3.4	0.78
MDS-UPDRS I (score 0–16)	12.6 ± 5.5	10.7 ± 5.3	<0.001
MDS-UPDRS II (score 0–52)	18.6 ± 8.8	18.5 ± 8.5	0.98
MDS-UPDRS III “off” (score 0–108)	38.7 ± 16.2	43.4 ± 7.1	0.003
MDS-UPDRS III “on” (score 0–108)	9.1 ± 7.1	10.1 ± 7.6	0.24
MDS-UPDRS IV (score 0–23)	8.6 ± 3.5	8.4 ± 3.4	0.60
Axial score “on” (score 0–16)	1.1 ± 1.6	1.0 ± 1.5	0.58
Axial score “off” (score 0–16)	4.5 ± 3.8	5.0 ± 3.9	0.23
MoCA (score 0–30)	26.3 ± 2.7	26.4 ± 3.1	0.64
ASBPD total (score 0–84)	7.7 ± 5.1	5.1 ± 0.4	0.003
Hypodopaminergic disorders subscore (score 0 to 20)	3.1 ± 2.5	2.8 ± 2.3	<0.001
Neuropsychiatric fluctuations subscore (score 0 to 8)	1.4 ± 1.5	0.7 ± 1.2	0.52
Hyperdopaminergic disorders subscore (score 0 to 56)	3.1 ± 2.9	0.8 ± 1.8	0.39
ICD subscore (score 0 to 28)	0.6 ± 1.1	0.5 ± 0.8	0.33
PDQ-39-SI (score 0 to 100)	33 ± 12	29 ± 12	0.03
Mobility	37 ± 20	36 ± 22	0.53
Activities of daily living	37 ± 19	38 ± 20	0.60
Emotional well-being	37 ± 18	29 ± 17	<0.01
Communication	28 ± 19	24 ± 18	0.02
Social support	15 ± 18	10 ± 15	<0.01
Cognition	34 ± 16	23 ± 15	<0.01
Stigma	35 ± 23	33 ± 23	0.20
Bodily discomfort	49 ± 21	41 ± 20	<0.01

Abbreviations: ASBPD = Arduin Scale of Behavior in Parkinson's Disease; ICD = impulse control disorder; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; PDQ-39-SI = Parkinson's Disease Questionnaire-39 Summary Index.

cognitive, psycho-behavioral symptoms, treatment doses, and quality of life score variations between baseline and post-operative evaluation at 12 months depending on the presence of pre-opRBD are presented in Tables 3–6.

STN-DBS resulted in a mean decrease of MDS-UPDRS III med-off scores compared to baseline (defined as the chronic effect of stimulation), by 52% in pre-opRBD+ ($p < 0.01$) and

by 54% in pre-opRBD- ($p < 0.001$), with no between-group difference (Table 3). MDS-UPDRS IV score significantly decreased by 37% ($p < 0.01$) in pre-opRBD+ and by 33% ($p < 0.01$) in pre-opRBD- with no between-group difference. STN-DBS also led to a LEDD total reduction compared to baseline in both groups (pre-opRBD+ $-52%$, $p < 0.01$; pre-opRBD- $-49%$, $p < 0.01$), with no between-group difference.

Table 2 Preoperative Clinical and Demographic Features of Patients With Parkinson Disease Who Are Candidates for Subthalamic Nucleus Deep Brain Stimulation, According to the Presence of Postoperative Follow-up 12 Months After Surgery

Characteristics	Patients without postoperative 12-month follow-up (n = 233)	Patients with postoperative 12-month follow-up (n = 215)	p Value
Age, y	60.3 ± 7.7	60.3 ± 7.1	0.93
Sex, male: female	158:75	142:73	0.69
Probable RBD	120 (51.5%)	122 (56.7%)	0.27
Total LEDD, mg/d	1,442 (965–1,588)	1,541 (1,000–1,746)	0.16
Dopamine-agonist LEDD, mg/d	368 (150–374)	370 (160–420)	0.22
Duration of disease, y	10.7 ± 4.1	11.4 ± 4.4	0.11
Duration since onset motor complications, y	5.8 ± 3.5	6.1 ± 3.5	0.38
MDS-UPDRS I (score 0–16)	12.2 ± 5.7	11.1 ± 5.1	0.03
MDS-UPDRS II (score 0–52)	18.8 ± 9.7	18.2 ± 7.3	0.93
MDS-UPDRS III “off” (score 0–108)	39.8 ± 17.1	42 ± 16.2	0.05
MDS-UPDRS IV (score 0–23)	8.2 ± 3.5	8.8 ± 3.3	0.05
Axial score “on” (score 0–16)	4.8 ± 4.0	4.6 ± 3.7	0.93
Axial score “off” (score 0–16)	1.1 ± 1.4	1.1 ± 1.8	0.55
MoCA (score 0–30)	25.8 ± 3.2	26.8 ± 2.3	0.005
ASBPD total (score 0–84)	6.87 ± 4.7	7.65 ± 5.1	0.12
PDQ-39 (score 0–100)	30.5 ± 13.10	31.2 ± 11.2	0.58

Abbreviations: ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; ICD = impulse control disorder; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; PDQ-39 = Parkinson's Disease Questionnaire-39; RBD = REM sleep behavior disorder.

MDS-UPDRS I and MDS-UPDRS II significantly decreased in both groups, yet no between-group difference of variation was observed. MoCA score decreased both in pre-opRBD– ($p < 0.05$) and in pre-opRBD+ ($p < 0.05$) after STN-DBS, but without any significant group differences.

Regarding psycho-behavioral features, hyperdopaminergic total subscores significantly decreased in both groups, with no between-group difference. There was no postoperative variation of hypodopaminergic total subscore in the pre-opRBD+ group, while it significantly worsened in pre-opRBD– ($p = 0.03$), but there was no significant between-group difference. ASBPD total score and nonmotor fluctuation subscores significantly decreased in both groups (Table 4).

PDQ-39-SI scores significantly decreased in pre-opRBD– (–16%, $p < 0.01$) and in pre-opRBD+ (–8%, $p < 0.01$), with no between-group difference. Activities of daily living and stigma subscores significantly decreased in both groups, whereas cognition and communication subscores only decreased in pre-opRBD+ ($p < 0.01$), although none of these variations significantly differed between groups. Bodily discomfort was the only quality of life subscore that, while significantly decreasing in both groups, decreased more significantly in the pre-opRBD+ group ($p = 0.04$) (Table 5).

At baseline, there was no difference between pre-opRBD+ and pre-opRBD– for any cognitive assessment except for CLOX copy, for which pre-opRBD+ patients presented statistically better scores compared to pre-opRBD– patients ($p = 0.003$), although this difference was not clinically significant because scores were in the normal range for both groups. There was no significant between-group difference for postoperative variation of attentional, instrumental, and memory functions assessed by the 11 cognitive tests, nor was there any between-group difference at postoperative evaluation for these tests (Table 6).

Multivariate analysis taking into account the effect of age, sex, LEDD, and MDS-UPDRS III “off” scores at preoperative evaluation confirmed that there was no difference of variation 12 months after STN-DBS between pre-opRBD+ and pre-opRBD– for MDS-UPDRS II and IV, MoCA, and ASBPD total and subtotal scores (Table 7).

Discussion

Among patients with PD who are candidates for STN-DBS, pre-opRBD+ patients were older, with milder motor

Table 3 Parkinsonian and Cognitive Symptoms and Quality of Life Before and After Bilateral Subthalamic Nucleus Deep Brain Stimulation in 215 Patients With Parkinson Disease, According to the Presence or Absence of Probable REM Sleep Behavior Disorder Preoperatively (pre-opRBD)

	pre-opRBD+ (n = 122)			pre-opRBD- (n = 93)			p Value	p ^b
	Baseline	12 months	% Change from baseline	Baseline	12 months	% Change from baseline		
MDS-UPDRS I (score 0-16)	11.7 ± 5.1	10.1 ± 5	-16% (-43; 25) ^a	10.2 ± 4.8	10.0 ± 5.3	-11% (-42; 25)	0.03	0.14
MDS-UPDRS II (score 0-52)	18.3 ± 7.2	15.8 ± 8	-15% (-10; 11) ^a	18 ± 7.4	15.7 ± 8.2	-13% (-45; 30) ^a	0.80	0.57
MDS-UPDRS III (score 0-108)								
med-off pre-op vs med-off/ stim-off post-op	39.7 ± 15.2	40.7 ± 15.9	2.7% (-17; 33)	45.1 ± 17.1	48 ± 18.2	1.7% (-18; 41)	0.01	0.63
med-on pre-op vs med-on/ stim-on post-op	10.1 ± 7.1	9.9 ± 7.2	15% (-45; 50)	10.2 ± 7	10.5 ± 8.6	0% (-44; 100)	0.78	0.64
med-off pre-op vs med-off/ stim-on post-op	39.7 ± 15.2	20 ± 11.4	-52% (-28; 65) ^a	45.1 ± 17.1	23. ± 13.6	-54% (-25; 67) ^a	NA	0.28
MDS-UPDRS IV (score 0-23)	8.9 ± 3.4	5.4 ± 3.2	-37% (-67; -9) ^a	8.7 ± 3.1	5.8 ± 3.1	-33% (-54; 10) ^a	0.77	0.43
MoCA (score 0-30)	26.9 ± 2.4	25.4 ± 3.7	-3% (-10; 0) ^a	26.8 ± 2.4	25.4 ± 3.1	-4% (-9; -2) ^a	0.90	0.85
Total LEDD, mg/d	1,341 (998-1,750)	799 (486-1,098)	-52% (-77; -25) ^a	1,333 (1,000-1,740)	562 (280-1,050) _a	-49% (-66; -17) ^a	0.75	0.22

Abbreviations: LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment.

^a Significant variation compared to baseline; p value: between-group comparisons of absolute values at baseline.

^b p: between-group comparisons of variation between baseline and 12 months after bilateral subthalamic nucleus deep brain stimulation.

symptoms, but with poorer nonmotor aspects of daily living, more hypodopaminergic psycho-behavioral symptoms, and decreased quality of life compared to pre-opRBD- patients at preoperative evaluation. Twelve months after STN-DBS, both pre-opRBD+ and pre-opRBD- patients had MDS-UPDRS IV score decrease (-37% and -33%, respectively), MDS-UPDRS III med-off decrease (-52% and -54%), and total LEDD decrease (-52% and -49%) after surgery, with no between-group difference. There was no between-group

difference for cognitive, psycho-behavioral, or global quality of life outcomes.

To our knowledge, this is the first study to assess motor and nonmotor outcomes of STN-DBS depending on the presence of probable preoperative RBD in a large multicentric cohort of patients with PD. So far, 2 prospective studies assessed the outcome of patients with PD with and without pre-opRBD and reported conflicting results. The first was conducted on

Table 4 Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) Before and After Bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) in 215 Patients With PD, According to the Presence or Absence of Probable REM Sleep Behavior Disorder Preoperatively (pre-opRBD)

	pre-opRBD+		pre-opRBD-		p Value	p ^b
	Baseline	12 months	Baseline	12 months		
ASBPD (score 0-84)	8.05 ± 5.2	6.14 ± 4.70 ^a	7.12 ± 4.8	5.09 ± 3.9 ^a	0.14	0.98
Hypodopaminergic disorders subscore (score 0-20)	3.16 ± 2.36	3.01 ± 2.07	2.26 ± 1.9	2.87 ± 2.3 ^a	0.003	0.06
Non-motor fluctuations subscore (score 0-8)	1.41 ± 1.45	0.78 ± 1.19 ^a	1.49 ± 1.29	0.66 ± 1.2 ^a	0.46	0.68
Hyperdopaminergic disorders subscore (score 0-56)	3.47 ± 3.27	2.35 ± 3.25 ^a	3.36 ± 3.20	1.55 ± 2.10 ^a	0.61	0.26
ICD subscore (score 0-28)	0.91 ± 1.17	0.64 ± 1.14 ^a	0.70 ± 1.04	0.47 ± 0.76	0.11	0.68

Abbreviation: ICD = impulse control disorders.

^a p < 0.05 for within-group comparison of absolute values between baseline and 12 months after STN-DBS; significant variation compared to baseline; p value: between-group comparisons of absolute values at baseline.

^b p: between-group comparisons of variation between baseline and 12 months after STN-DBS.

Table 5 Quality of Life Before and After Bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) in 215 Patients With Parkinson Disease, According to the Presence or Absence of Probable REM Sleep Behavior Disorder Preoperatively (pre-opRBD)

	pre-opRBD+ (n = 122)			pre-opRBD- (n = 93)			p Value	p ^b
	Baseline	12 months	%	Baseline	12 months	%		
Summary Index (score 0–100)	32.7 ± 11.8	30.1 ± 12.4	-8% (-31; 13) ^a	29.1 ± 10.0	25.6 ± 13.2	-16% (-50; 7) ^a	0.04	0.48
Mobility	38.2 ± 21.1	36.7 ± 22.1	-4% (-32; 42)	37.5 ± 19.3	32.4 ± 21.3	-21% (-46; 33)	0.70	0.29
Activities of daily living	38.2 ± 19.6	30.5 ± 18.4	-20% (-42; 23) ^a	39.7 ± 18.8	27.2 ± 17.5	-30% (-67; 10) ^a	0.76	0.20
Emotional well-being	35.6 ± 17.1	33.4 ± 17.6	-11% (-33; 38)	31.0 ± 16.6	30.7 ± 18.2	0% (-33; 37)	0.04	0.49
Communication	26.8 ± 19.3	30.7 ± 20.6	0% (-40; 67) ^a	25.1 ± 18.5	25.6 ± 19.7	0% (-50; 50)	0.59	0.28
Social support	14.1 ± 16.4	16.2 ± 17.9	0% (-100; 50)	9.2 ± 13.9	13.3 ± 17.7	-50% (-100; 25)	0.01	0.66
Cognition	34.6 ± 16.8	28.2 ± 18.1	-13% (-57; 14) ^a	24.8 ± 14.8	22 ± 15.7	-8% (-62; 50)	0.0001	0.19
Stigma	35.2 ± 22.3	25.4 ± 20.1	-33% (-67; 0) ^a	34.4 ± 22.6	21.4 ± 19.7	-37% (-89; 0) ^a	0.79	0.33
Bodily discomfort	50.6 ± 21.1	36.1 ± 20.6	-26% (-50; 0) ^a	39.6 ± 18.5	32.2 ± 21.2	-25% (-60; 25) ^a	0.0001	0.048

^a Significant variation compared to baseline; p value: between-group comparisons of absolute values at baseline.
^b p: between-group comparisons of variation between baseline and 12 months after STN-DBS.

41 patients with PD screened for probable preoperative RBD (12% of patients) using a semi-structured clinical interview.²⁰ The second was conducted on 50 patients with PD, and RBD diagnosis was confirmed preoperatively by night polysomnography (48% of patients).²¹

These studies did not report any significant difference between patients with PD with and without pre-opRBD at baseline for motor symptoms assessed with UPDRS III “off,” whereas in our study pre-opRBD+ patients had better motor performance than pre-opRBD- patients. These findings are in contrast with the concept that patients with PD with RBD usually have greater motor disabilities and more axial impairment.^{36,37} Because we observed no difference at baseline for composite axial signs between pre-opRBD+ and pre-opRBD-, it is possible that we selected a subgroup of patients with PD with RBD as good candidates for surgery, because those with axial signs such as freezing of gait or postural instability were not meeting STN-DBS criteria, thereby excluding a range of patients with PD with associated RBD. Conversely, Zibetti et al.²⁰ suggested that more severe axial symptoms preoperatively in pre-opRBD patients with PD could account for the lower percentages of improvement of motor symptoms after STN stimulation that they reported in this group at 1 and 3 years.

The second study compared UPDRS II and UPDRS III absolute scores at baseline (med-on condition) and postoperatively (med-on/stim-on condition 12 months after STN-DBS) in patients with PD with and without polysomnography-confirmed RBD.²¹ Aligned with our results, they report a significant improvement of UPDRS III “on” score in both groups, without between-group difference. Moreover, UPDRS II “on” score

significantly improved in pre-opRBD+, whereas it remained stable in pre-opRBD-.²¹

Global psycho-behavioral outcomes after STN-DBS did not differ between groups and total ASBPD score was improved in both groups. These results are in line with the Bargiotas et al.²² study showing that patients with PD with RBD have greater apathy and depression symptoms than those without RBD at baseline, whereas no difference remained 1 year after STN-DBS. In the whole population of PD, the effect of STN-DBS on psycho-behavioral hypodopaminergic symptoms is debated, with some studies reporting improvement^{13,38} and others describing worsening.^{14,39-41}

Previous studies did not assess hyperdopaminergic outcomes after STN-DBS in patients with PD with and without pre-opRBD. The lack of association with ICD preoperatively in our study in the RBD+ group goes against the described association between RBD and ICDs in PD, and could be due to the selection of a nonrepresentative “less severe” subgroup of patients with PD with RBD as candidates for STN-DBS.^{42,43} Both groups improved after surgery for total hyperdopaminergic ASBPD and for ICD subscores.

No between-group difference was found for cognitive outcomes 12 months after surgery. Previous studies assessing STN-DBS outcome of PD with RBD did not investigate detailed cognitive functions, but only cognitive dimension of PDQ-39. In the study by Bargiotas et al.,²² no between-group difference was observed after STN-DBS for the cognitive dimension of PDQ-39. These findings probably reflect the selection of a specific subgroup of RBD+ patients fulfilling criteria for STN-DBS, with better cognitive profile compared

Table 6 Cognitive Functions 12 Months Before and After Bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) in 215 Patients With Parkinson Disease, According to the Presence or Absence of Probable REM Sleep Behavior Disorder Preoperatively (pre-opRBD)

	pre-opRBD+ (n = 122)			pre-opRBD- (n = 93)			p Value	p ^b	p ^b
	Baseline	12 months	% Change from baseline	Baseline	12 months	% Change from baseline			
Attention									
SDMT (score 0–150)	42.4 ± 9.3	37.9 ± 9.8	-11% (-22; 1) ^a	44.9 ± 10.5	39.3 ± 10.3	-13 (-22; -2) ^a	0.12	0.37	0.50
Memory									
Digit Span Forward and Backward									
Digit Span Forward (score 0 to 16)	9.1 ± 2.37	8.6 ± 2.01	-8% (-17; 11)	9 ± 2.25	8.7 ± 2.04	0 (-17; 12)	0.81	0.79	0.61
Digit Span Backward (score 0–16)	7.2 ± 2.17	6.7 ± 1.96	0% (-20; 14) ^a	7.5 ± 2.50	6.9 ± 2.28	-11 (-24; 14)	0.45	0.53	0.63
Subtests 16-item free/cued recall test									
Total free recall trial (score 0–48)	15.3 ± 0.99	15.1 ± 1.16	0% (-6; 0)	15 ± 1.90	14.7 ± 1.85	0 (-7; 0)	0.33	0.09	0.24
Total cued recall score (score 0–48)	45.8 ± 3.39	43.7 ± 6.17	-2% (-6; 2) ^a	45.6 ± 4.6	43.2 ± 6.7	0 (-8; 0) ^a	0.76	0.58	0.51
10/36 spatial recall test									
Total free recall score (score 0–30)	14.12 ± 5.64	14.29 ± 4.90	0% (-23; 29)	14.6 ± 4.46	13.8 ± 4.33	0 (-33; 27)	0.52	0.60	0.21
Delayed free recall trial (score 0–10)	5.31 ± 2.18	5.3 ± 3.18	0% (-39; 34)	5.24 ± 2.17	4.95 ± 1.93	0 (-40; 50)	0.84	0.42	0.58
Executive function									
D-KEFS color–word interference test									
Inhibition (number of errors)	1.37 ± 1.62	2.03 ± 0.27	-2% (-48; 86) ^a	1.49 ± 1.76	2.41 ± 3.29	-2.5% (-40; 86) ^a	0.55	0.64	0.78
Inhibition/switching (number of errors)	1.91 ± 1.84	2.20 ± 1.94	4%.6% (-55; 93)	1.93 ± 2.27	2.42 ± 1.61	6.8% (-45; 73)	0.32	0.73	0.74
Oral letter–number sequencing task									
Baseline task, s	6.91 ± 2.38	7.28 ± 3.01	0% (-14; 27)	7 ± 2.8	8 ± 2.93	12.5% (-9; 33) ^a	0.83	0.15	0.11
Alternating task, s	39.8 ± 21.8	43.2 ± 22.2	8%.8% (-10; 37)	39.4 ± 26	40.4 ± 20.5	8.8% (-9; 33)	0.93	0.44	0.77
Errors, n	0.76 ± 1.10	0.69 ± 1.11	-55% (-100; 33)	0.53 ± 0.96	0.7 ± 1.07	-66.6% (-100; 0)	0.97	0.62	0.77
Switching cost	6.34 ± 4.22	6.46 ± 3.43	10.1% (-15; 45)	6.2 ± 4.05	5.4 ± 2.77	0.75% (-37; 25)	0.84	0.06	0.22
Language									
Animal fluency test (1 minute)	21.5 ± 5.3	18.2 ± 5.2	-13% (-33; 0) ^a	21.5 ± 5.7	18.6 ± 6.22	-13.3% (-30; 2) ^a	0.96	0.67	0.60
Boston Naming Test (score 0–15)	12.5 ± 2.17	12.52 ± 2.13	0% (-7; 8)	12.24 ± 2.71	12.0 ± 2.88	0% (-13; 7)	0.53	0.21	0.17
Visuospatial function									
CLOX clock drawing									
Draw (score 0–15)	13.3 ± 1.77	13.27 ± 1.74	0% (-8; 8)	13.16 ± 2.18	12.87 ± 2.07	0% (-7; 8)	0.70	0.22	0.90
Copy (score 0–15)	14.37 ± 1.0	14.07 ± 1.0	0% (-7; 0) ^a	13.73 ± 1.43	13.75 ± 1.16	0% (-7; 8)	0.003	0.10	0.16
Benton judgement of line orientation test (score 0–15)	12.1 ± 2.06	12.2 ± 2.48	0% (-8; 15)	12.2 ± 2.01	11.5 ± 0.31	0% (-15; 8) ^a	0.80	0.09	0.052

Abbreviation: SDMT = Symbol Digit Modalities Test.

^a Significant variation compared to baseline; p value: between-group comparisons of absolute values at baseline.

^b p: between-group comparisons of variation between baseline and 12 months after STN-DBS.

Table 7 Multivariate Analysis of Between-Group Comparison of Variation Between Baseline and 12 Months After Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) Adjusted on Age, Sex, Preoperative Levodopa Equivalent Daily Dose (LEDD), and Preoperative Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III "Off" Scores

	Coefficient	$p > z $	95% CI
MDS-UPDRS I	-1.140	0.18	-2.819; 0.537
MDS-UPDRS II	-0.019	0.77	-2.945; 2.191
MDS-UPDRS IV	-0.191	0.75	-1.393; 1.012
MoCA	-0.345	0.38	-1.129; 0.438
ASBPDP total score	-0.043	0.94	-1.299; 1.211
Hypodopaminergic disorders subscore	-0.679	0.05	-1.375; 0.016
Neuropsychiatric fluctuations subscore	0.109	0.59	-0.298; 0.518
Hyperdopaminergic disorders subscore	-1.588	0.25	-2.272; 0.903
ICD	0.055	0.74	-0.279; 0.391

Abbreviations: ASBPDP = Ardouin Scale of Behavior in Parkinson's Disease; CI = confidence interval; ICD = impulse control disorder; LARS = Lille Apathy Rating Scale; MoCA = Montreal Cognitive Assessment; PDQ-39 = Parkinson's Disease Questionnaire-39 for quality of life.

to what is generally reported in RBD. Indeed, cognitive impairment has been reported in patients with PD with RBD compared to patients with PD without RBD and with controls,⁴⁴ and more particularly visuo-perceptive alterations seem to be specifically associated with RBD either idiopathic or secondary to PD.⁴ Moreover, pre-opRBD+ and pre-opRBD- patients did not differ for attentional tasks at baseline or at postoperative evaluation, but both groups presented a significant postoperative decrease compared to baseline for SDMT, with no between-group difference for variation. Our results are in line with attention/concentration impairment previously reported after STN-DBS⁴⁵ and suggest that pre-opRBD+ patients fulfilling STN-DBS criteria do not have a greater risk for increased attentional impairment 1 year after surgery compared to pre-opRBD- patients.

In both groups, global quality of life improves after surgery with no between-group differences. However, while pre-opRBD+ patients have worse global quality of life preoperatively, it does not differ from pre-opRBD- patients 12 months after STN-DBS.

A number of limitations of this study must be noted. First, the lack of polysomnography-confirmed diagnosis of RBD could lead to some patients with PD having been misclassified. Yet, in order to increase the sensitivity of the clinical diagnosis, 2 different screening tools were combined to detect the

presence of symptoms of RBD: the RBD-IQ and the RBD-SQ. The latter showed a moderate to high sensitivity and specificity (0.842 and 0.962, respectively) using a cutoff ≥ 6 .²⁵ Furthermore, the limited access to video-polysomnography in clinical practice limited this examination on such an important multicentric cohort. Another limitation is that RBD status of patients was not controlled after STN-DBS, though STN-DBS has been reported to have an effect on RBD symptoms and could modify their prevalence postoperatively.^{46,47} Indeed, RBD symptoms may fluctuate along the evolution of PD,³⁶ but in spite of these clinical variations, the loss of muscle atonia during REM sleep, which is the polysomnographic feature of RBD, appears to be a long-lasting marker in PD.⁴⁸ Thus, a specific long-term trait seems to be associated with RBD, possibly in relation with a specific pattern of neurodegeneration, leading us to assess RBD as a predictor for STN-DBS outcome in that study. The lack of data regarding the location of electrodes and stimulation measures should also be acknowledged and could interfere with postoperative results. However, we noted in our whole population an improvement of 52% for motor MDS-UPDRS scores in the "off" medication state, a reduction of 36% for dyskinesia, and a reduction of antiparkinsonian drugs by approximately 36% after STN-DBS. Those results are close to the classically observed motor improvements of STN-DBS treatment, justifying the correct location of electrodes in this population.⁹ It should also be acknowledged that, while we report the largest cohort available in a study focusing on the predictive role of probable RBD before STN-DBS, there are limits as to the inferences that this study will support given the limited sample of baseline patients with 12 months follow-up. Moreover, these results are based on an early analysis 1 year after STN-DBS, and the follow-up of the whole cohort 3 and 5 years after surgery will bring more light on the question of the long-term motor and nonmotor prognosis associated with the presence of preoperative probable RBD.

Altogether, our results suggest that the presence of probable RBD preoperatively is not associated with different motor, cognitive, or global quality of life outcomes 1 year after STN-DBS. Total psycho-behavioral symptoms were also similarly improved in both groups. STN-DBS improves quality of life in patients with PD regardless of the presence of pre-opRBD. Thus, although the presence of RBD has been previously reported to be associated with a more severe phenotype of PD, it does not seem to constitute a marker of risk of poor outcome after surgery in patients with PD eligible for STN-DBS. Further studies, assessing long-term outcomes associated with the presence of RBD preoperatively 3 years and 5 years after surgery, will improve our comprehension of the specific prognosis associated with the presence of RBD in patients with PD who are candidates for STN-DBS.

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Disclosure

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Appendix 1 (continued)

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Appendix 1 (continued)

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Appendix 1 (continued)

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B590

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